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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,977	NGUYEN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-16,45,48,51-53,56-59,61-63 and 65-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11-16,45,48,51-53,56-59,61-63 and 65-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/10,3/31/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78 are pending and under examination in the application.

Withdrawn Rejection

In view of the amendments to the claims and applicants' arguments the 35 USC 112, 1St paragraph (new matter); 2nd paragraph and 35 USC 102 (b) over Guinto rejections have been withdrawn.

Information Disclosure Statement

The information disclosure statement filed on 3/31/10 and 7/21/10 has been considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection Necessitated by Amendment

New Matter Rejection

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, step (e) testing the identified protease(s) or biologically active portion thereof for cleavage and inactivation of an activity of the target protein that contains the substrate sequence thereby identifying a protease mutein or a biologically active portion thereof that inactivates an activity of a target protein that is involved with the disease or pathology is not supported in the as-filed specification.

MPEP 2163.06 clearly states that applicants point out where in the original disclosure the new amendments to the claims appear. (See also the lack of written description rejection below.)

Written Description Requirement

For claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, the specification fails to provide a written description for a (candidate) protease mutein that inactivates an activity of a target protein the inactivation of which can ameliorate a disease or pathology. The general statements in the specification are not a detail description of the invention. The Examples do not disclose (candidate) protease mutants that ameliorate any kind of diseases such as the claim any cancer disease or AIDS (HIV). The detail description provided in Example 8 of the instant specification describes a method of cleaving the different proteins e.g., TNF, VEGR **involved** in different disease or pathologies. The cleaving enzyme or protein however, has not been shown to be effective in the treatment of the variously claim disease(s). None of the description in the Example describes a disease that has been treated by the protease. The specification simply recites the involvement of the specific target protein to the different diseases due to the cleavage of the substrate protein. There is no description as to the target protein being useful to treat the disease of at times unknown etiology as cancer or for any types of cancer. In this regard attention is drawn to the newly submitted prior art, Trapani (Genome Biology, 2001) at e.g., page 6, last paragraph

which discloses that despite their biological importance, granzymes are still relatively poorly studied and many important questions remain to be answered. The nature of the synergy between perforin and granzyme - that is, the mechanism by which granzymes are released from the target cell's endosomes - remains poorly understood. Caspase-independent cell-death pathways are very important, because they allow CTLs to kill cells in which caspases have been blocked by viral inhibitors, such as the cytokine response modifier A (crmA) expressed by poxviruses. Again, the nature of these pathways has not been elucidated. Granzymes other than A and B doubtless have many functions other than in apoptosis, and the generation of further gene knockout mice should help to cast light on this area of research. It will also be fascinating to learn more about the regulation of granzyme function mediated by novel serpins. These studies could have major implications for our understanding of immune homeostasis (for example, the regulation of CTL numbers following an infection), and of effector responses to viral disease and cancer.

Furthermore, the specification fails to describe the claim method of step (e) testing the identified protease(s) or biologically active portion thereof for cleavage and inactivation of an activity of the target protein that contains

the substrate sequence thereby identifying a protease mutein or a biologically active portion thereof that inactivates an activity of a target protein that is involved with the disease or pathology. It is not apparent from the disclosure description as to type or kind of testing of any identified protease, if any, that has been applied to any or all kinds of target protein involved in any type of disease or pathology.

Response to Arguments

Applicants state that firstly, the Examiner's attention is directed to the instant amendments of the claims that remove reference to the identification of a candidate therapeutic. Secondly, it is submitted that the instant claims are not directed to either the proteases, nor to methods of treatment of a disease or condition by such proteases, the claims are directed to methods of screening proteases to identify mutants that cleave particular target proteins, target proteins involved in a disease or pathology, such that cleavage inactivates their activity, and by virtue of inactivation of such activity, a disease or pathology could be treated. Thus, a description of the actual in vivo treatment is not relevant to the claimed methods, which are screening methods. The instant claims are

directed to a screening method for identifying from among a library of mutant proteases those that inactivate an activity of a target protein involved in a disease or pathology. The identified proteases then can serve as candidate therapeutics for treating the disease or pathology.

In reply, there is nothing in the office action that has required applicants for a description of in vivo treatment. Rather, a description of the (direct) effect of cleavage of a target protein resulting in the treatment of the target protein involvement with the numerous different claimed diseases. Thus, while the claims are drawn to screening, as argued, however, the claims are not limited simply to screening. Rather, to screening, identifying and testing for the protease' binding to the target, that results in the claimed amelioration of the numerous claim diseases.

Applicants state that in practicing the method, one does not need a priori knowledge of a protease that inactivates an activity of a protein, or knowledge that the protease can treat the disease or condition. That is the point of the screening method. By practice of the method, proteases can be identified that inactivate an activity of a target protein. These proteases

can be used as in vivo therapeutic agents. Their actual use in methods of treatment is not claimed, and is therefore not relevant to instant claims.

In reply, the specification has not described an identified protease or testing for cleavage of a target protein. Lacking such description, it follows that the description of inactivation of a target protein by an unidentified protease would not result in the treatment, albeit, this seems to be incidental to the method.

Applicants state that the specification provides detailed description for identifying targets whose inactivation could ameliorate (treat) the symptoms of a disease or pathology. For example, on page 23, lines 12-22: Proteins targeted for cleavage and inactivation are identified by the following criteria: 1) the protein is involved in pathology; 2) there is strong evidence the protein is the critical point of intervention for treating the pathology; 3) proteolytic cleavage of the protein will likely destroy its function. Cleavage sites within target proteins are identified by the following criteria: 1) they are located on the exposed surface of the protein; 2) they are located in regions that are devoid of secondary structure (i.e.

not in 13 sheets or helices), as determined by atomic structure or structure prediction algorithms; (these regions tend to be loops on the surface of proteins or stalks on cell surface receptors); 3) they are located at sites that are likely to inactivate the protein, based on its known function. Cleavage sequences are e.g., four residues in length to match the extended substrate specificity of many serine proteases, but can be longer or shorter. In addition, at least 45 exemplary target proteins and the disease or pathology in which they are involved are provided in Table 1 on page 9. Therefore, it respectfully is submitted that the specification describes in detail the identifying characteristics of target proteins for screening mutant proteases. In this case the modified proteases are screened for cleavage of the target protein. The specification provides exemplary target proteins, such that one of skill in the art would understand and be able to identify a target protein involved in a pathology or disease. The specification describes the methods used to identify protease muteins that cleave a substrate sequence in a target protein involved with pathology by identifying those protease mutants from among a library of mutants that have increased cleavage activity and/or altered specificity for a substrate sequence in the target substrate. The identified muteins are tested for their ability

to inactivate, by cleavage, the target protein. It is these methods that are the subject of the instant claims, and that are taught in the specification. The methods provide a way to produce and identify the muteins. The claims are not directed to the mutein proteins, or to methods of treatment using the muteins. Thus, demonstration of the actual in vivo treatment is irrelevant.

In reply, as stated by applicants above the claims are not drawn to the protease product but to a screening method. Hence, the argued criteria of identifying a target protein involved in the numerous claimed diseases are of no moment to the screening of a protease. Applicants are merely reinstating the definitions or criteria of the target or its cleavage site but the exemplification is nil or if any to a single target protein.

For claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected for lacking written description. The specification describes granzyme as the sole cleaving enzyme used in the method. Claim 1, for example, encompass an enormous variation of enzyme muteins, even for granzyme alone which contain numerous allelic variants. It is not known how many

allelic variants of granzyme, let alone of the huge protease exist and what the structures even look like for each of any proteases. Thus, the genus of proteases encompassed by the claims as employed in the method is too large and structurally diverse. However, the specification only describes a single species of this genus e.g., granzyme, with particularity but these species are not deemed as representative of said genus. It is noted that the MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated: "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as

words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents" of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiefs, 984 F.2d at 1171, 25 USPQ2d 1601; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398. In addition, it is noted further that the Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small

organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004). It is asserted, however, that the instant claims are not adequately described in the specification to claim the broad and structurally diverse genus of the compounds use in the method. The claims lack written description and a skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that are allelic variants. This is true even for the single granzyme, let alone for any enzymes of no claim distinguishing features as use in the broad method steps. The method steps broadly comprises the steps of producing any library of protease mutein, contacting and measuring any cleavage activity of any enzyme at any sites for any kind of target protein. At the time of applicants' invention it is known that in biotechnology art one species cannot be extrapolated to another due to the numerous unforeseeable reaction or interactions of protease-substrate. For example, Rosen et al (20020086811) discloses at e.g., paragraph [0018] that caspases are among the most specific of proteases, with an unusual and absolute requirement for cleavage after aspartic acid. (The only other eukaryotic protease known to have a similar specificity is

the serine protease granzyme B, a mediator of granule-dependent cytotoxic T lymphocyte-mediated apoptosis). Recognition of at least four amino acids NH2-terminal to the cleavage site is also a necessary requirement for efficient catalysis. The preferred tetrapeptide recognition motif differs significantly among caspases and explains the diversity of their biological functions. Their specificity is even more stringent: not all proteins that contain the optimal tetrapeptide sequence are cleaved, implying that tertiary structural elements may influence **substrate** recognition. **Cleavage** of proteins by **caspases** is not only specific, but also highly efficient. The strict specificity of caspases is consistent with the observation that apoptosis is not accompanied by indiscriminate protein digestion; rather, a select set of proteins is **cleaved** in a coordinated manner, usually at a single site, resulting in a loss or change in function.

Response to Arguments

Applicants argue that the claims are drawn to a method of screening a library of mutant proteases, and not to products. Thus, the genus to which the Examiner refers is a genus of methods that include the elements as recited in the instant

claims, not a genus of resulting proteases. The Examiner's comments appear to be premised on the notion the method can only be performed if one knows all of the structural and functional attributes of the protease to generate protease mutein.

In reply, it is appreciated that the claims are method claims. However, the compounds used in the method must affect the method in a manipulative sense and not simply amount to reciting the product in the method. There is nothing in the Office action that alludes for the method to perform only if "**all of the structural and functional attributes of the protease**" are claimed. Rather based on the instant detail description of the single protease and target protein and prior art knowledge, screening can only be achieved given the mutations done on a parent protease. The mutated protease has to be screened against a target protein specific only for said protease in order to identify mutant(s) with increased activity relative to the parent protease. A skilled artisan to date has not made any priori statements or extrapolation of correlating a single species to the genus as claim. This is due to the high uncertainty in the art, where one variable(s) cannot be predictably attributed to the success or failure of an

experiment. This is clearly evident from the Rosen reference, cited above which discloses at e.g., paragraph [0018];

> That caspases are among the most specific of proteases, with an unusual and absolute requirement for cleavage after aspartic acid. (The only other eukaryotic protease known to have a similar specificity is the serine protease granzyme B, a mediator of granule-dependent cytotoxic T lymphocyte-mediated apoptosis). Recognition of at least four amino acids NH2-terminal to the cleavage site is also a necessary requirement for efficient catalysis. The preferred tetrapeptide recognition motif differs significantly among caspases and explains the diversity of their biological functions. Their specificity is even more stringent: not all proteins that contain the optimal tetrapeptide sequence are cleaved, implying that tertiary structural elements may influence **substrate** recognition. **Cleavage** of proteins by **caspases** is not only specific, but also highly efficient. The strict specificity of caspases is consistent with the observation that apoptosis is not accompanied by indiscriminate protein digestion; rather, a select set of proteins is **cleaved** in a coordinated manner, usually at a single site, resulting in a loss or change in function.

Cf. with the working example in the instant specification.

Applicants assert that by following the method, mutant proteases are identified that have increased activity and/or altered substrate specificity for a substrate sequence, such that the protease cleaves and inactivates a target protein containing the sequence.

In reply, applicants' failure to provide representative species, instead of a single species, raises a questionable description or possession of the genus claim method using broadly any kind of protease against any type of target protein.

Applicants assert that a protease(s) is used as a scaffold for modification; a collection with a variety of modifications is provided and the collection is screened for the ability to cleave a particular target. No structure/function knowledge is needed; the activity can be evolved into the protease.

In reply, again the specific embodiments in the specification e.g., the working example do not identify a scaffold protease for modification. Applicants are further referred to the above responses as to the argued structure/function knowledge. (Cf. with the instant working example which appears to be a structure/function method.)

Applicants submit that the specification provides ample and detailed description of protease scaffolds (including lists, see, e.g., Table 2, of protease scaffolds) that can be used in the methods. As described in the specification, these scaffolds, regardless of their original structure (e.g. sequence) or

function (e.g. substrate specificity) can be used to generate muteins of the desired specificity and activity, i.e. muteins that cleave and inactivate a target protein involved in a disease or pathology.

Applicants assert that the specification describes in great detail the scaffold proteases that can be used in the method. The specification describes relevant, identifying characteristics of such proteases, sufficient for use of the proteases in the method as claimed. For example, at page 17, lines 25-32 the specification describes the process for choosing a scaffold for use in the method: In another embodiment of the invention, scaffold proteases are chosen using the following requirements: 1) The protease is a human or mammalian protease of known sequence; 2) the protease can be manipulated through current molecular biology techniques; 3) the protease can be expressed heterologously at relatively high levels in a suitable host; and 4) the protease can be purified to a chemically competent form at levels sufficient for screening. In addition, the specification describes exemplary proteases for use in the method. For example, Table 2 sets forth many protease scaffolds that can be used in the method.

In reply, applicants' arguments, general statements in the specification and/or definitions do not replace the requirement of the law that applicants describe in detail that which is claimed to show possession of the claims being sought. Furthermore, a listing or selection of every possible protease scaffold or target does not constitute a written description of every species in a genus. It would not "reasonably lead" those skilled in the art to any particular species. In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967). That the specification describes an exemplary protease is not controverted. The issue is the lack of written description for the enormous scope of the genus claim being sought for patenting.

The written description requirement implements the principle that a patent must describe the technology that is **sought to be patented**; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). Further, the written description requirement promotes the progress of the useful arts by ensuring that patentees adequately describe their inventions in their patent

specifications **in exchange for the right to exclude others from practicing the invention for the duration of the patent's term.** To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. See MPEP 2163. Herein only a single protease, granzyme modified at specific positions for mutein identification is described in the working example. As evident from the Rosen reference above, one cannot make a priori statement based only on the single species, granzyme.

Claim Objections

Claim 66 is objected to because it depends upon cancelled claim 64. Appropriate correction is required.

Applicants have not responded to the above objection. However, instead of issuing a non-responsive action and in the interest of compact prosecution, the objection is maintained. Applicants must respond to this objection in their response to this office action to avoid the holding of non-responsive

response in the next office action thus prolonging prosecution of the application.

Claim Rejections - 35 USC § 102

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 102(b) as being anticipated by Lien et al(Combinatorial Chemistry and High Throughput Screening, 1999)(as evidenced by Shi et al, USP 20020197701) for reasons of record as repeated below.

For claims 1-7, 13, 16, 45, 51-53, 57-59, 61 and 67-78, Lien discloses at e.g., pages 73-75 a method of identifying serine proteases using targeted combinatorial mutagenesis of serine proteases with N mutations (e.g., Fig. 1, page 74). The method comprises producing sizeable libraries of mutant enzymes (N mutations), contacting the library with a substrate and identifying the mutant. Screening and selecting methods both depend not only on the activity and specificity of mutant proteins but also on their individual expression levels (e.g., page 77, col. 1, first complete paragraph). Lien discloses at e.g., page 77, first incomplete paragraph, quantitative assessments of cleavage made by monitoring the hydrolysis

(inactivation as claim) of a set of synthetic peptides esters in a colorimetric plate assay. Lien discloses at e.g., page 73 that the mutant enzyme is useful for therapy as in blood coagulation.

For claim 13, Lien discloses mutants with improved cleavage of at least 62.

For Claim 56, Lien discloses that phage displayed proteins can be subjected to in vitro selection procedures, e.g., page 77, first incomplete paragraph, col. 1.

For claims 16, 45, 57, Lien discloses at e.g., page 74, chemical mutagenesis, passage through bacterial mutator strains and PCR. (See also e.g., paragraph bridging pages 76-77.)

For claim 52 Lien discloses at e.g., page 76, col. 2 "in vivo" selection.

For claim 61, Lien discloses at e.g., page 86, col. 2, first incomplete paragraph, granzyme B.

For claims 69, 72, 75 and 78, Lien et al discloses at e.g., page 76, col. 2, and last incomplete paragraph chromogenic substrates.

For claims 68, 71, 74 and 77 Lien discloses at e.g., page 78, col. 1-col.2, under Screening Methods, tetrapeptide with P1=Phe.

The claim inactivation of a target protein involved with a disease or pathology in a mammal that ameliorate a disease is a property inherent or implicit to the teachings of Lien. [This is evident from the teachings of Shi et al at e.g., paragraph [0003]. Shi states that members of the serine **protease** family which play important roles in a range of cellular functions and which have demonstrated causative roles in human **diseases** include tissue-type plasminogen activator and thrombin (thrombosis and blood clotting), urokinase-type plasminogen activator (cancer and metastasis), trypsin and elastase (emphysema and liver **disease**) and angiotensin converting **enzyme** (hypertension).

Response to Arguments

Applicants acknowledge that the methods described in Lien et al. include 1) producing a library of mutant proteases; and 2) selecting and screening the proteases for altered cleavage activity and specificity. But argue that Lien et al. does not disclose any target proteins involved in a disease or pathology for which cleavage inactivates the target protein. Applicants also recognize that Lien discloses target proteins but only casein that can be used to select for any active mutants, and chromogenic substrates that include a substrate sequence, which

are used to assess the specificity profile of the mutants. There is no disclosure in Lien et al. that the target protein being cleaved in the methods is involved in a disease or pathology nor that cleavage inactivates an activity thereof. Lien et al., does, not, therefore, disclose methods in which the identified protease mutant cleaves a target protein involved in a disease or pathology. Nor is there any disclosure that such inactivation can ameliorate the disease or pathology.

In reply, the species disclosed by Lien is sufficient to meet the broad claimed unnamed or unstructured protease to any inactivated target protein as broadly claimed. The claimed property of the target protein is a property inherent to the target protein of Lien. Furthermore, as applicants stated above the claim is to screening method for protease not to the target protein, let alone its function. Thus, the property of the target protein is irrelevant and would inherently ensue since Lien teaches the same effect achieved by the specific protease i.e., inactivation or cleavage of the target protein. Notwithstanding this, Lien teaches at e.g., page 73, col. 1:

> "…{i}t is useful to be able to generate proteases with new and desirable cleavage specificities. Such enzymes….. could have practical applications in biotechnology…. therapy (modulation of zymogen cascades, such as blood coagulation)….

Furthermore, the substrate inherent property of involvement in diseases by virtue of its cleavage by the enzyme to inactivate it wherein the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, cytokine and etc. is recited in the claim preamble. The claim preamble is accorded, if any little weight as the preamble is used only to state a purpose or intended use for the target protein. This is the more true since the specification has not taught any disease amelioration attributed to the substrate upon its inactivation by a protease protein. Rather, as shown by the detailed description in the working example of the single granzyme protease, screening and identification of the mutant granzyme are the only method steps described in detail.

Applicants additionally argue that Lien et al., does not disclose the target proteins recited in e.g., claim 63.

In reply, attention is drawn to Lien at e.g., paragraph bridging pp. page 86-87 wherein Lien discloses a truncated human growth hormone substrate for proteolytics cleavage, which is included in claim 63.

Applicants state that Shi et al., is directed to the identification of wild-type serine proteases and nucleic acids encoding them. Shi et al. state, in paragraph [003]:

> Members of the serine protease family which play important roles in a range of cellular functions and which have demonstrated causative roles in human diseases include tissue- type plasminogen activator and thrombin (thrombosis and blood clotting), urokinase-type plasminogen activator (cancer and metastasis), trypsin and elastase (emphysema and liver disease) and angiotensin converting enzyme (hypertension).

Applicants assert that Examiner has either misread the claims or misread Shi et al. Applicnats state that it is not the protease mutein that is involved in the disease or pathology, but the target protein. As discussed above, Shi et al. is directed to the identification of wild-type serine proteases. Shi et al. does not disclose any methods of producing and identifying mutant proteases that cleave and inactivate a target protein. Shi et al. states that the serine proteases can be involved in cellular functions and disease. Shi et al. is not referring to a target protein, but instead to the serine protease. Thus, Shi et al. does not address, in any way, the limitation in the claims that the mutein protease inactivates a target protein involved in a disease, thereby ameliorating the disease.

In reply, as applicants stated at page 27 of the instant REMARKS, claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. Rosemount Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983).

So read, the specification at e.g., page 52, lines 1 recite a caspase, as the specific target protein. Thus, the unnamed or unstructured protease can also cleave another protease as the target protein.

Thus, the target protein taught by Shi is the same target protein as claimed that are involved in the different diseases as stated by applicants above. Please note that the diseases taught by Shi are the same diseases as listed at e.g., Table 1, page 12 of the instant specification.

Claims 1-5, 7, 9, 11, 13-16, 48, 51-53, 58-59, 61-63, 65 and 67, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Guinto et al (Proc. Natl. Acad. Sci. USA, 96, pp.

1852-1857, March 1999) for reasons of record as reiterated below.

Guinto et al discloses at e.g., page 1852, Materials and methods heading up to page 1853, including fig. 1 and fig. 2 a method of identifying a mammalian protease by providing from a database a total of 284 enzymes including enzymes involved in degradation (trypsin, chymotrypsin, and elastase), fibrinolysis (plasmin, tissue plasminogen activator, and urokinase), cellular-mediated immunity (granzymes and mast cell proteases), embryonic development (Easter and Snake), the vitamin K-dependent enzymes of blood coagulation (thrombin, factor Xa, factor IXa, and activated protein C) and complement proteases (C1r, Cls, MASP-I, and MASP-2). The variability of residue 225 in coagulation factor Vlla is analyzed. Guinto at e.g., page 1854, col. 2, provide mutants which are contacted with chromogenic and natural substrates such as fibrinogen, protein c and antithormbin III. It was found that the nature of residue 225 influences the catalytic activity of the enzyme up to 8,000-fold (Fig. 2). Mutants (N, as claim) with Tyr and Phe are associated with the highest specificity. The ability to interact with the natural inhibitor antithrombin III follows the same pattern as the other ligands and is compromised up to 60,000-

fold in the Ile mutant. The similarity of the activity profiles in Fig. 2 suggests that the nature of residue 225 influences a structural domain recognized by small chromogenic substrates, natural substrates, and inhibitors alike.

The claim ability of the candidate mutant as a therapeutic for treatment of the disease associated with the target substrate is a property considered inherent to the prior art mutant serine proteases. The ability of the mutant protease to catalyze the target protein such as fibrinogen or protein C will result in the inactivation of the target hence its amelioration of the disease associated with fibrinogen or protein C. Furthermore, the claim function of the target protein e.g., a signaling protein that regulates apoptosis is a function inherent to the prior art target protein.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same..." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594,

596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). See MPEP 2112.

Response to Arguments

Applicants argue that the target proteins cleaved by the mutant thrombin proteases in Guinto et al. are activated, not inactivated. Thus, Guinto et al. does not disclose at least two important limitations in the methods of the instant claims 1) cleavage of a substrate sequence in the target protein inactivates an activity of the target protein and 2) inactivation of the target protein by the mutein protease can ameliorate a disease or pathology.

In reply, Guinto teaches above inhibitors i.e., inactivation of target protein as claimed. The resultant effect of said inhibition would inherently ameliorate a disease or pathology to which the target protein is involved. The function of the target protein involvement with the numerous diseases is irrelevant to the screening protease that binds or inhibits said target protein. Please see further the discussion above as to the amelioration of the disease.

Applicants argue that Guinto et al. does not disclose the method as claimed in claim 1. But recognize that Guinto et al. only discloses fibrinogen, protein C, and antithrombin III as target proteins. But further argue that none of these are a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis, as recited in claims 1 and 59. Nor are they included among the target proteins recited in claim 63.

In reply, Guinto discloses the step of providing a library from the library of enzymes obtained from a database. Guinto further teaches above the variability (mutants, as claimed) of residue 225 in coagulation factor Vlla is analyzed. Guinto at e.g., page 1854, col. 2, provide mutants which are contacted with chromogenic and natural substrates such as fibrinogen, protein c and antithormbin III (step 2, as claimed). It was found that the nature of residue 225 influences the catalytic activity of the enzyme up to 8,000-fold (Fig. 2). Mutants (N, as claim) with Tyr and Phe are associated with the highest specificity. The ability to interact with the natural inhibitor antithrombin III follows the same pattern as the other ligands and is compromised up to 60,000-fold in the Ile mutant. (Steps

3-4, as argued above.) The similarity of the activity profiles in Fig. 2 suggests that the nature of residue 225 influences a structural domain recognized by small chromogenic substrates, natural substrates, and inhibitors alike.

Applicants are referred to above as to the limitation of the target being in the preamble i.e., that the fibrinogen or protein C and antithrombin of Guinto are not a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis, as recited in claims 1 and 59.

Claim Rejections - 35 USC § 103

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lien et al in view of either Harris et al (The Journal of Biological Chemistry)(I) or (Current Opinion in Chemical Biology(II) and Waugh et al (Nature Structure Biology) for reasons of record as reiterated below.

Lien is discussed supra. Lien does not disclose the enzyme as granzyme (albeit suggests said granzyme, above) and the substrate as caspase (elected species).

Harris et al discloses at page 27364, identification of in vivo targets of granzyme B based on the elucidation of the substrate specificity of granzyme B. For example, Harris et al. teaches that based on the substrate specificity of granzyme B, certain caspases (caspases 3 and 7), based on their sequences, are more likely substrates then other caspases. Harris et al., also teaches that based on the sequence specificity of granzyme B, nuclear lamin A and nuclear poly(ADP)ribose polymerase (PARP) are potential in vivo substrates for granzyme B. Harris et al. I also teaches that amino acid position Arginine 192 is a structural determinant of specificity of granzyme B, since granzyme B mutations R192E and R192A exhibit reduced hydrolysis of the optimal tetrapeptide substrate Ac-IEPD-AMC and non-optimal tetrapeptide substrate Ac-IKPD-AMC compared to the wild-type enzyme. Harris also discloses at e.g., pages 27372 up to and 27373:

> ….{T]here is a functional relationship between the preferential substrate sequence of granzyme B and the activation site of members of the caspases (Fig. 5D). Indeed, studies have shown that granzyme B cleaves and activates several **caspases involved in apoptosis.** Our data on the substrate specificity of granzyme B suggest that caspase 3 and caspase 7 are preferentially activated during apoptosis. Knowledge of the extended substrate specificity of granzyme B allows for the proposal of additional targets of granzyme B during apoptosis. The substrate specificity of caspase 6 matches that of granzyme B, suggesting that both enzymes cleave the same substrates. Several proteins

> known to be cleaved during apoptosis, such as nuclear lamin A….
> The identification of their specificity will further expand our knowledge of the role that granzymes play in **cytotoxic, lymphocyte-mediated cell death.**

Harris (II) throughout the article, at e.g., pages 127-129, basically discloses the same method as Harris (I).

Waugh discloses at page 762 that granzymes are a vital component of the cytotoxic lymphocyte's ability to induce apoptosis, contributing to rapid cell death of a tumor or virally infected target cell by the cleavage of downstream substrates and the activating cleavage of caspases.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use as the serine protease granzyme in the method of Lien. Harris teaches that granzyme is a substrate for caspases or caspases can act as substrate depending on its sequence. Accordingly, one would have a reasonable expectation of success in using other serine protease, such as granzyme as taught by Lien as the other serine proteases. Furthermore, one would also have a reasonable expectation of success in using granzyme as an enzyme for caspase substrate depending upon the sequence contain in each enzyme as taught by Harris above. One would be motivated to use either caspase or granzyme to act as enzyme or substrate due to

the dual role each enzymes exhibits depending upon the sequence that is contained therein. Furthermore, caspase and granzyme are only the two most specific of proteases, with an unusual and absolute requirement for cleavage after aspartic acid.

Response to Arguments

Applicants present the same arguments to Lien as above. Applicants further argue that none of Harris et al. I, Harris et al. II and/or Waugh et al., singly or in any combination thereof, cure the Lien deficiencies. It is argued that Harris et al. I teach elucidation of the substrate specificity of wild-type rat granzyme B, and the putative identification of in vivo substrates based on knowledge of the substrate specificity. There is no teaching or suggestion for using granzyme B as a scaffold produce a mutein protease with increased cleavage activity and/or altered its substrate specificity for a target, such that the mutein inactivates an activity of the target protein, nor any methods for doing so. Nor is there any suggestion that inactivation of the target protein by cleavage with the mutein protease can ameliorate the disease or condition that the target protein is involved in. Harris et al. I, in the abstract, states that: I states that:

> Mutagenesis of arginine 192 to glutamate reversed the preference for negatively charged amino acids at P3 to positively charged amino acids. The preferred substrate sequence matches the activation sites of caspase 3 and caspase 7 and thus is consistent with the role of granzyme B in **activation** of these proteases during apoptosis. [Emphasis added].

The Examiner herself notes, on page 21, line 1 of the Office Action, that Harris et al. I teach that granzyme B cleaves and activates several caspases involved in apoptosis. Harris et al. II does not, therefore, teach or suggest a method that a) includes a step of testing a mutant protease (or biologically active portion thereof) for cleavage and inactivation of an activity of a target protein; or b) the target protein used in the methods is involved with a disease or pathology in a mammal, or that c) such inactivation of the target protein ameliorates the disease or pathology.

In reply, Harris is not used for the purpose as argued since Lien teaches the mutations that can be done to a protease protein. Rather, Harris I is employed for its teachings of the specific enzyme granzyme B (which is also taught or suggested by Lien). It would be within the ordinary skill in the art to use the specific enzyme

granzyme as taught by Harris in the method of Lien since Lien also teaches, or at least suggests, said particular protease.

The preamble of the claim recites "regulates" apoptosis to which activation would be encompassed. Furthermore, as stated above, the preamble is accorded, if any, little weight. It is of interest to note Harris' findings with the same findings in the instant specification at e.g., page 53, lines 18-20;

"at low concentrations the mutant **activates** caspase-3 by cleaving at the activation sequence (SEQ ID NO:4)…"

(Emphasis added.)

Applicants present the same arguments for Harris II and Waugh as for Harris I above. The same reasons/responses to Harris I above apply to Harris II and Waugh.

Thus, the combined teachings of the prior art would lead one having ordinary skill in the art at the time the invention was made. The claimed method steps are routine steps in screening and identifying a **specific** mutant from a library of mutants that binds to a **specific** target protein to identify a protease mutant with improved property. The method is nothing more than a predictable result expected in screening protease proteins.

Double Patenting

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, for example, of copending Application No. 12/005949 ('949 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim method is similar, if not nearly identical to the method of the '949 application. The subject matter of the instant and the '949 applications overlap in scope.

Response to Arguments

Applicants request deferral of resolution of this rejection. Applicants assert that it is not possible to assess whether claims at allowance in each application will overlap requiring a terminal disclaimer until there is an indication of allowable subject matter in at least one application, and for certainty, both applications.

In reply, in the absence of a terminal disclaimer, the rejection is maintained.

NO claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA

WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639